

### REMARKS

Consideration of the amendments presented herein and reconsideration of all grounds for objection and rejection are respectfully requested. Claims 24-32 are pending in the application.

Claims 1-23 are hereby cancelled without prejudice. Claims 19, 20, and 21 (numbering corrected herein) are withdrawn by the Examiner from consideration by the Examiner as being drawn to a non-elected invention.. This leaves claims 24-32 in this case for examination.

New claims 24-32 correspond to the following cancelled claims: 24~4; 25~5; 26~7; 27~9; 28~10; 29~14; 30~16; 31~17; and 32~18.

### *Restriction/Election*

The election of the Group I, claims 1-18, 22 and 23, designated by the Examiner as Group I, is hereby affirmed. It is noted that the claims in the Groups designated by the Examiner as being drawn to the non-elected invention are claims 19, 20 and 21, as described on page 2 of the Office Action, rather than claims 21 and 22, as later indicated on page 3 of the Office Action.

### *Claim Rejections - Double Patenting*

The Examiner has rejected claims 1-19 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,379,943.

To overcome this rejection for the presently pending claims, Applicant agrees to provide, upon a notification of allowance of claims, a terminal disclaimer in compliance with 37 CFR 1.321(c). The "conflicting" referenced patent is commonly owned with the present application.

*Claim Rejections - 35 USC 102*

The Examiner has rejected claims 1, 2, 3, 11, 13, 17 and 22 under 35 U.S.C. 102(b) as being anticipated by Kaleko et al. (WO 97/25446) ("Kaleko"). For reasons unrelated to Kaleko, Applicants have cancelled all of these claims, without prejudice, except for claim 17 in the present application. The following discussion generally explains why Kaleko is not relevant to any claim in the present application, and concludes with reasons that claim 17 is allowable in view of Kaleko.

A limitation of the present invention, as defined in the independent claims, is that both the first and second nucleic acid sequences each comprise a head-to-head ("hth") ITR junction. As discussed in the specification, such hth ITR arrangement when in both sequences that were combined was found to enhance recombination efficiency. In one embodiment, the nucleic acid was in the form of a shuttle plasmid, and such plasmid was shown to result in increased efficiency, in separate experiments, both for site-specific Cre recombination and for homologous recombination (see Example 11, starting page 64, and in particular page 66, lines 13-16, and page 67, lines 4-6, and Table 4).

Another aspect of the presently claimed invention is that the first and the second nucleic acid sequences combine by means of homologous recombination.

In distinct contrast to the hth ITR of the present invention, Kaleko discloses that a terminal protein (TP) attached to an ITR improves efficiency. The presence of the TP, and the disclosed structure of Kaleko's nucleic acid constructs, precludes an hth ITR being present in these constructs. It is noted that Figures 7, 10, 19, and 24 generally show each ITR in association with a TP molecule in linear structures (also see pages 11-12). Since Kaleko regards the use of TP, there is no clear indication that any of the structures shown in the figures were known or used by Kaleko without such TP endings. Thus, Kaleko does not disclose the hth ITR of the present invention.

As further proof, the Kaleko disclosure states, in a number of places, that its nucleic acid structures may have one or the other, not both ITRs present. For instance, on page 13, regarding the first polynucleotide, "In addition to the adenoviral 5' or 3' ITR, . . ." indicates both are not present (see also page 12, lines 9-12, of Kaleko). In contrast, as noted above, the present invention claims both ITRs present to form an hth ITR junction for reasons indicated above and documented in the disclosure.

As to the means of recombination, Kaleko practices the use of a recombinase (See page 7, last paragraph). In contrast, the claims of the present invention utilize homologous recombination.

Finally, regarding claim 17, Kaleko discloses using a mutation of the packaging signal in the "helper" virus (starting on page 12, last paragraph, to page 13). This, it is believed, is a mechanism to result in less production of packaged helper virus. In contrast, claim 17 *rescues* an adenoviral gene mutation *into* the recombinant adenoviral vector. Thus, the adenoviral gene mutation survives recombination and may be studied, for instance, to determine its function or other characteristics.

For the above reasons, the rejection of claim 17 in view of Kaleko is improper and reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 1, 2, 6, 8, 11, 13, 15, 22 and 23 under 35 USC 102(b) as being anticipated by Bett et al. (1994, Proc. Natl. Acad. Sci. USA 91:8802-6). These claims are cancelled in the present amendments, and this rejection is not applicable to the presently pending claims.

The Examiner has rejected claims 1, 2, 6, 8, 11, 13, 15, 22 and 23 under 35 USC 102(b) as being anticipated by Bett et al. (1993, J. Virology 67:5911-21). These claims are cancelled in the present amendments, and this rejection is not applicable to the presently pending claims.

*Claim Rejections - 35 USC 112, first paragraph*

Claims 1-19, 22 and 23 stand rejected under 35 USC 112, first paragraph, as containing subject matter not which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention.

As to these rejections, Applicant, at the time of filing the earliest application upon which priority is claimed for this application, was in possession of the invention as required by the present written description guidelines. This invention is directed to methods, systems and kits to produce adenoviral vectors. The invention is not directed to specific compositions. This, and the high level of art in this field must be kept in mind with regard to this basis for rejection.

For example, on page 9 of the 09/11/2002 Office action, it is stated that "Claim 4, 16, 17, and 18 recite adenovirus DNA having a deletion or mutation of a gene." First, as to claim 4, this regards a deletion of a packaging signal. This is not a gene, but is a part of the adenoviral sequence required in *cis* for packaging. As disclosed on pages 36-37, the deletion of the packaging signal results in the inability to package (to produce infectious virus) for the nucleic acid sequence with such deletion.

Second, as to claim 16 (now ~ 30), the specification provides to one of skill in the art what the meaning and the scope are of a deletion of the fibre gene in the first nucleic acid sequence. The Examiner is referred to pages 5, 18-19, and 26, among others. The deletion of the fibre gene provides for the insertion in its place, for instance, of a loxP site and an ampicillin resistance gene. These are inserted and used for clearly known functional purposes (i.e., in recombination and selection, respectively). This is not a case in which, for instance, a claim is directed to a genus of fibre gene sequences. The claim is for a method having clear functional aspects and results, and the exact nature and sequence of the fibre gene is not of consequence to the claimed invention. The fibre gene is well-characterized and locatable based on knowledge in the art.

Third, as to claims 17 and 18 (now ~ 31 and 32), the adenoviral genes being cited are merely *being rescued by means of the method being claimed*. Such genes are simply “passengers” being moved about by the methods, vectors systems, and kits of the present invention. It is believed that the exact sequences of such genes are not needed for one of skill in the art to recognize that the Applicant is in possession of the methods, vector systems, and kits of the present invention.

The Examiner is referred to the application, particularly to pages 23-24, 34 (starting at line 21) to 37, line 19, 67, lines 4-10, and 70, line 8 to 71, line13, to better appreciate the scope of the present claims as amended.

As to the claimed methods, vector systems, and kits of the present invention, it is believed that the multiple examples of vectors and combinations of these amply demonstrate a representative number of species, and relevant identifying characteristics, so as to provide an adequate written description of the presently claimed invention. Accordingly, regarding the above bases for rejection, the claims as amended are believed to overcome the 35 USC 112/1 written description rejections.

Also, as to the part of the rejection based on the requirement that the plasmids of the claims must be known, be readily available to the public, or must be obtainable by a repeatable method disclosed in the specification, or that a deposit of biological material is made, Applicants assert that all of the plasmids claimed in the present invention are obtainable by repeatable methods disclosed in the specification, in the parents, and that such disclosed methods are further supported by references incorporated by reference and the level of ordinary skill in the art. Accordingly, Applicant believes that deposits are not required.

If certain terms or clauses remain in the claims as amended which the Examiner finds still present a rejection under 35 USC 112/1, the courtesy of a telephone call to the Attorney for Applicant will be most appreciated, in order to provide an opportunity to find acceptable claim language in view

of the claim types, the specification, and the knowledge in the field. The toll-free telephone number for Attorney for Applicant is 888-416-1464.

**Claim Rejections - 35 USC 112, second paragraph**

Claims 1-23 stand rejected as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." By making the changes detailed below, and shown in the claims as herein amended, it is urged that these grounds for rejection have been addressed and overcome.

The term "insufficient" has been replaced with the term "incapable." On page 36, lines 10-11, when discussing the "two plasmid" technique of adenovirus vector construction, it is stated, "each plasmid alone is incapable of generating infectious virus." The term so substituted is definite, and based on the examples in the disclosure, particularly in view of the ample data provided (see tables in application showing numbers of plaques obtained), and the high level of skill in the art, one of ordinary skill in the art is reasonably apprised of the scope of the invention.

Claim 5 (~ claim 25) has been amended to remove the grammatically unnecessary "of."

Claim 5 (~ claim 25) has been amended to replace "extending beyond said packaging signal" with "3' of said packaging signal." This is supported based on the description of the location of the packaging signal, approximately 194-358 bp, per page 35, line 5, and the known location of E1 early transcription genes, most or all of which are 3' of the packaging signal. It is noted that for the adenovirus sequence described on page 35, lines 2-6, only about 93 base pairs exist 5' of the packaging signal between this and the left ITR. This is insufficient coding for any protein of typical length, and further supports the amendment to "3' of said packaging signal."

Claim 14 (~ claim 29) has been amended to remove "as optionally needed."

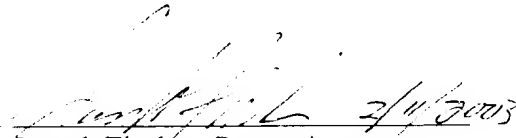
Also, to avoid any unintentional limitation in the scope of the claims, the word "replicable" was removed. It is noted that this word can be ambiguous when applied to recombinant vectors given cells such as the 293 cell. For instance, not to be limiting, recombinant vectors lacking sequences encoding E1 adenoviral proteins may nonetheless replicate in a 293 cell (which provides such E1 proteins). However, such recombinant vectors would not replicate in 'typical' cells that do not provide such E1 proteins. It is noted that both E1+ (such as when the vector had been manipulated at E3, and is E3-) and E1- recombinant vectors are disclosed and fall within the scope of the present invention. The E1+/E3- vectors can replicate in 'typical' cells, whereas E1-/E3+ vectors cannot. In that neither the presence or lack of E1, nor the replicability, is not critical to the novelty of the present invention, the word "replicable" has been removed from the claims to clarify the claims.

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All claims having either been placed in condition for allowance or cancelled, expedited passage of this case to issuance is respectfully solicited.

**Applicant requests that the Examiner call the undersigned, at 888-416-1464, if clarification is needed on any aspect of this response, or if the Examiner believes that any valid basis of non-patentability remains after entrance and consideration of the remarks and amendments presented herein.**

Respectfully submitted,

  
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